An Introduction to Chronic Hepatitis B
Partnering to Act on Hepatitis B Virus in Your Community

Ann Moore, NP

LIVER HEALTH AWARENESS INITIATIVE hepatitis B

Objective and Agenda

OBJECTIVE

- Understand the importance of screening for and managing chronic hepatitis B (CHB) in your patients

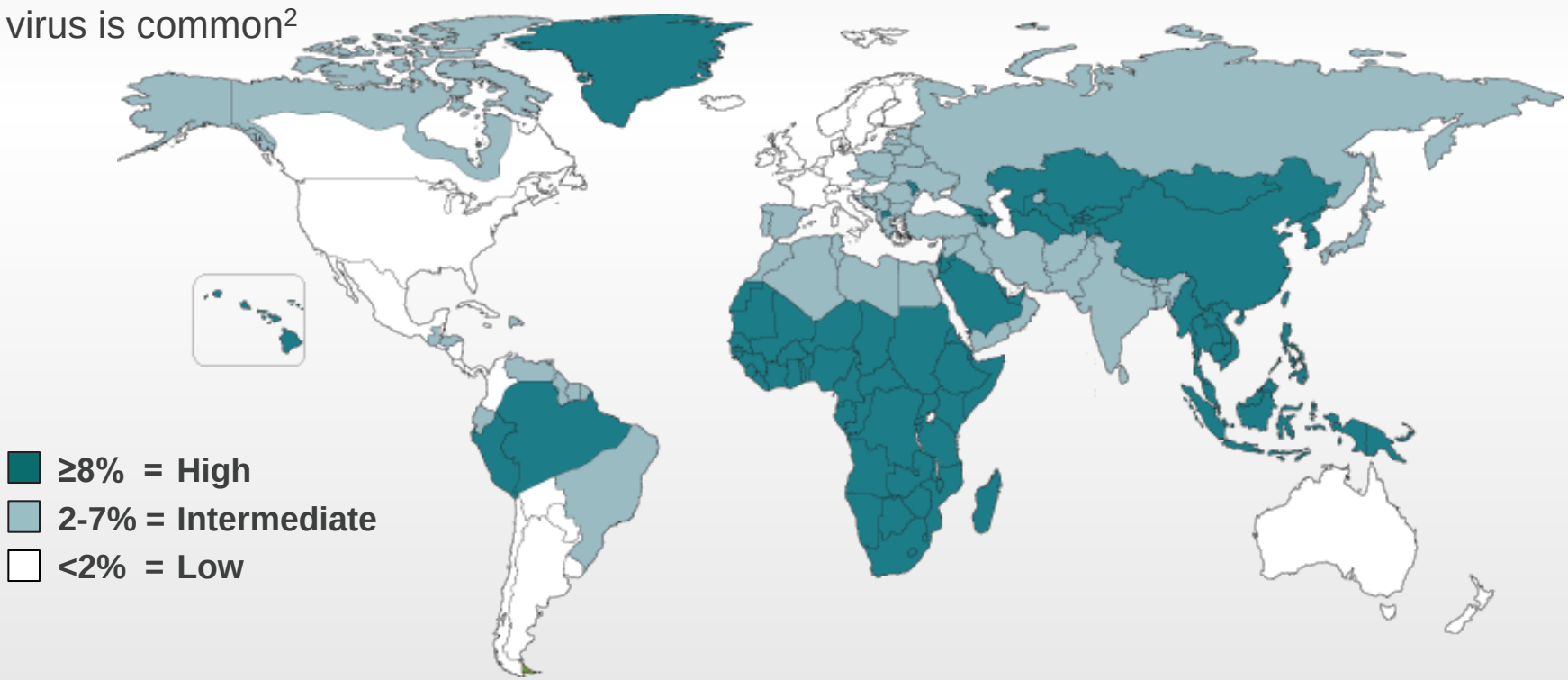
AGENDA

- Overview of CHB
  - Scope of the problem
  - Clinical course and consequences
- Management of CHB
  - Screen
    - Who should be screened for CHB
    - How to interpret results
  - Evaluate
    - What to do when a patient tests positive for CHB
  - Counsel
    - Ways to counsel a patient with CHB
  - Treat
    - What are the goals of antiviral treatment

Overview of CHB

CHB is a Global Health Issue With Increasing Importance in the United States

- Approximately 350 million people worldwide have CHB[1,2]
- High prevalence areas include regions of[2,3]:
  - Asia
  - Africa
  - Eastern Europe
  - The Middle East
  - Latin America
  - The Caribbean
- Most people in the US who have CHB were born in regions of the world where the virus is common[2]



1. WHO. Hepatitis B Fact Sheet. http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed October 11, 2011.
2. CDC. *Morb Mortal Wkly Rep*. 2008;57:1-20.
3. CDC. *Morb Mortal Wkly Rep.* 2005;54:1-39.

Prevalence of CHB in the United States

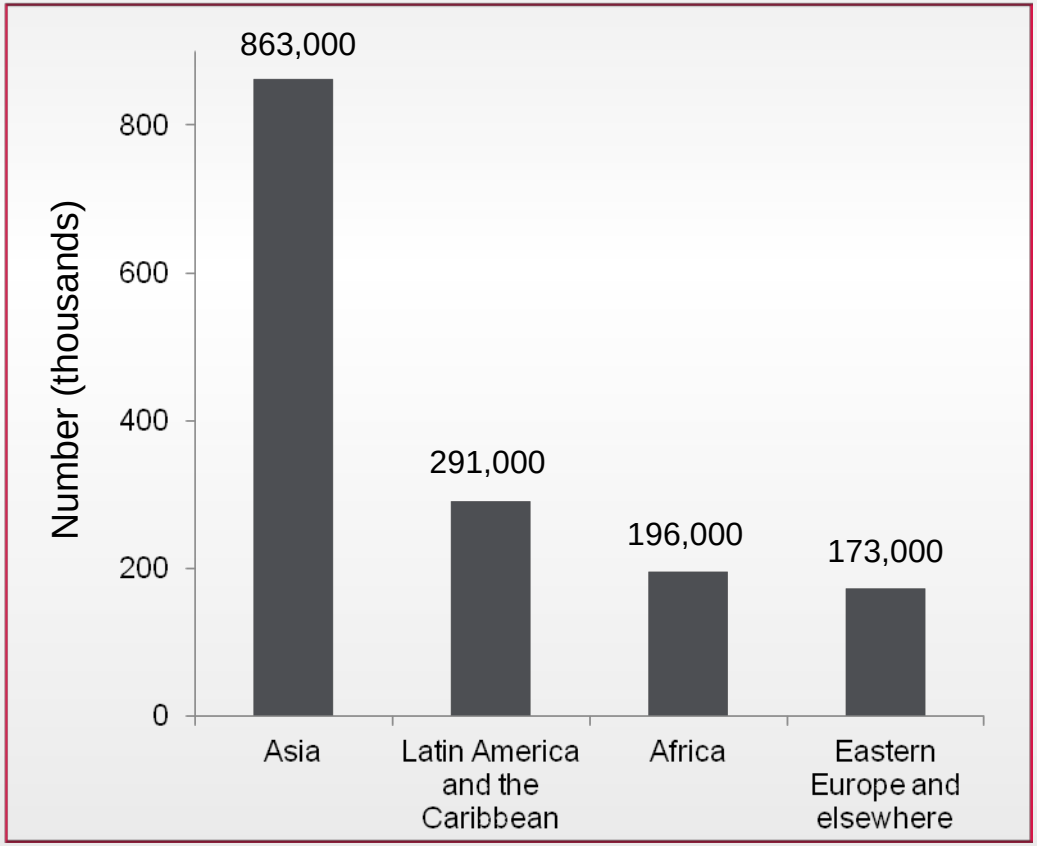
2 Million People in the US Have CHB[1]

"During the last 2 decades, the influx of foreign-born persons immigrating to the United States from areas of high endemicity…has contributed to an increased presence of CHB, particularly in urban areas and communities with a high immigrant population."[2]

EB Keeffe

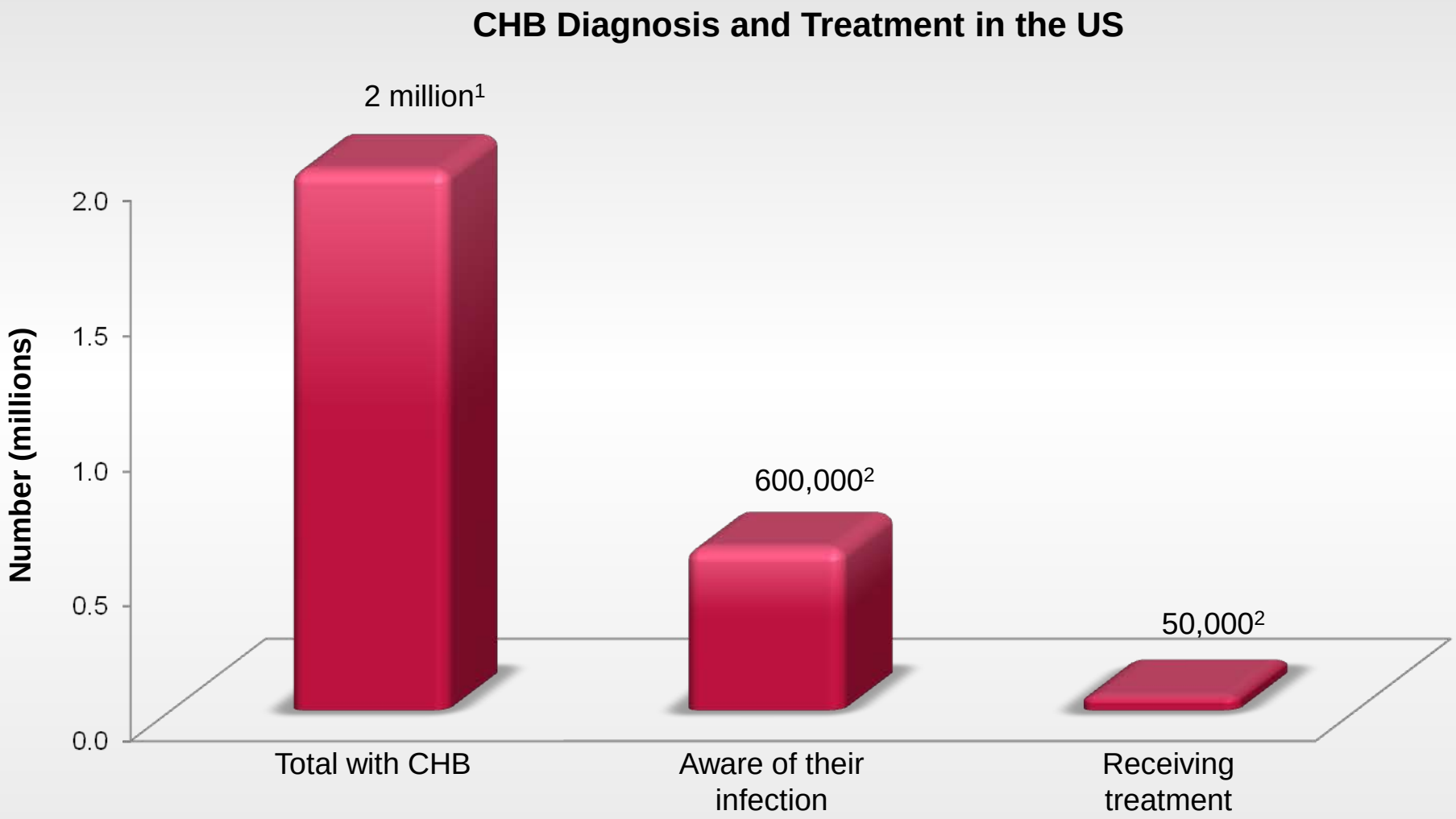
1.5 Million of These Are Foreign Born[3]

Estimated prevalence of CHB in foreign-born persons in the US by region of origin[3,4]



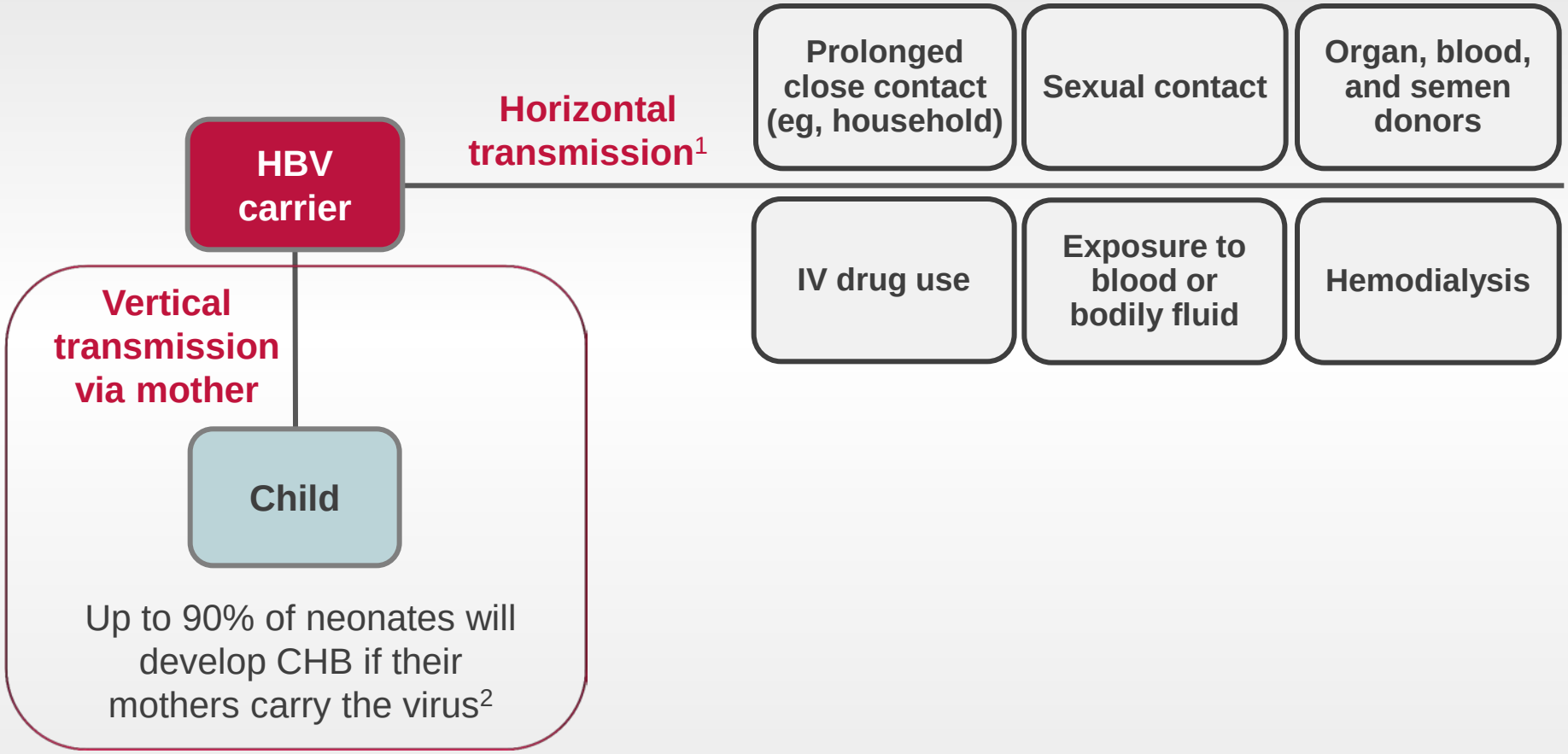
1. Cohen C et al. *J Viral Hepatitis*. 2008;15:12-13.
2. Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.
3. Kim WR. *Hepatology*. 2009;49:S28-S34.
4. Welch S et al. *Hepatology*. 2008;48(Suppl):687A.

The Majority of Americans With CHB are Undiagnosed and Untreated



1. Cohen C et al. *J Viral Hepat.* 2008;15:12-13.
2. Cohen C et al. *J Viral Hepat*. 2011;18:377-383.

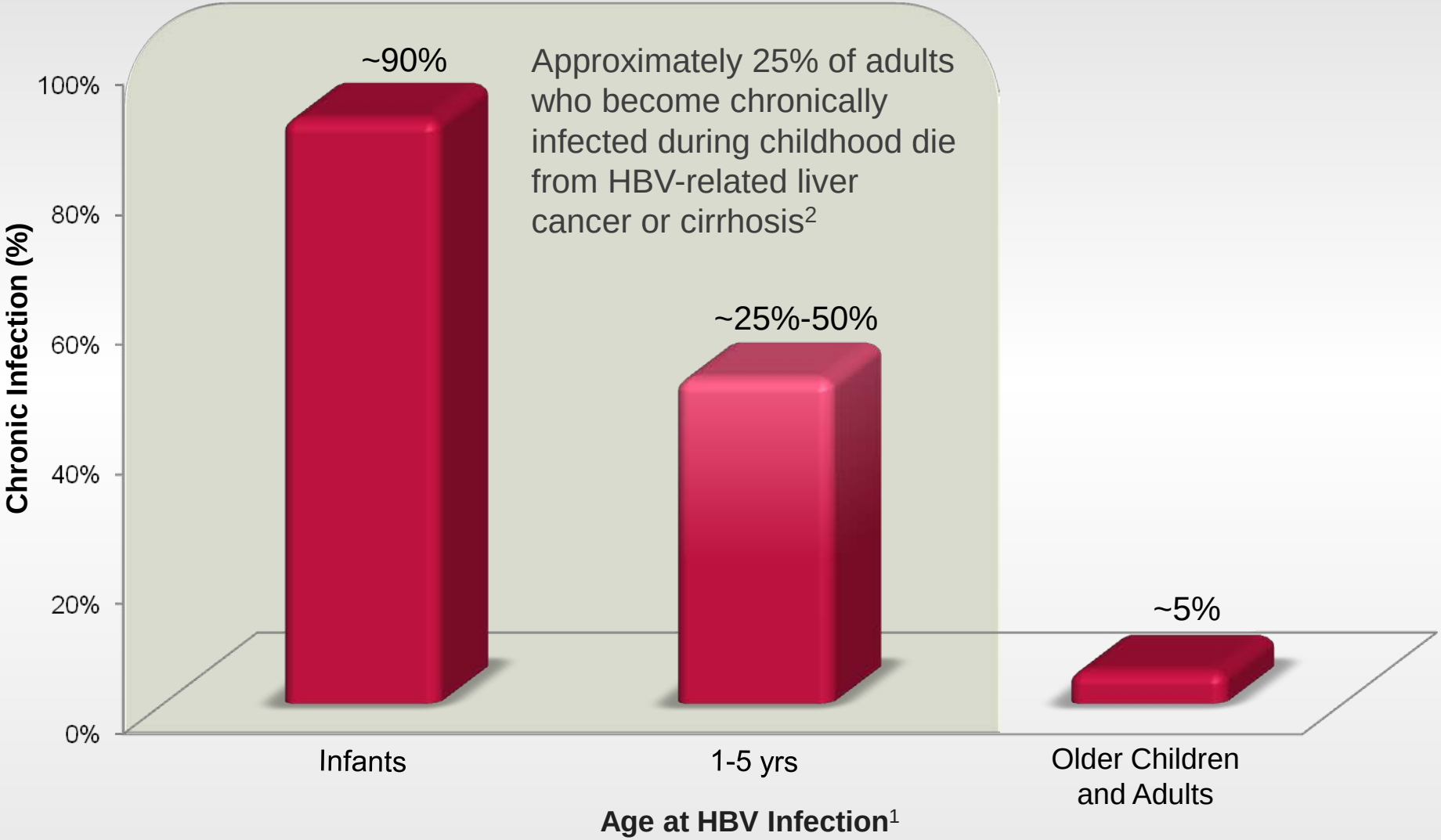
Modes of HBV Transmission



HBV, hepatitis B virus.

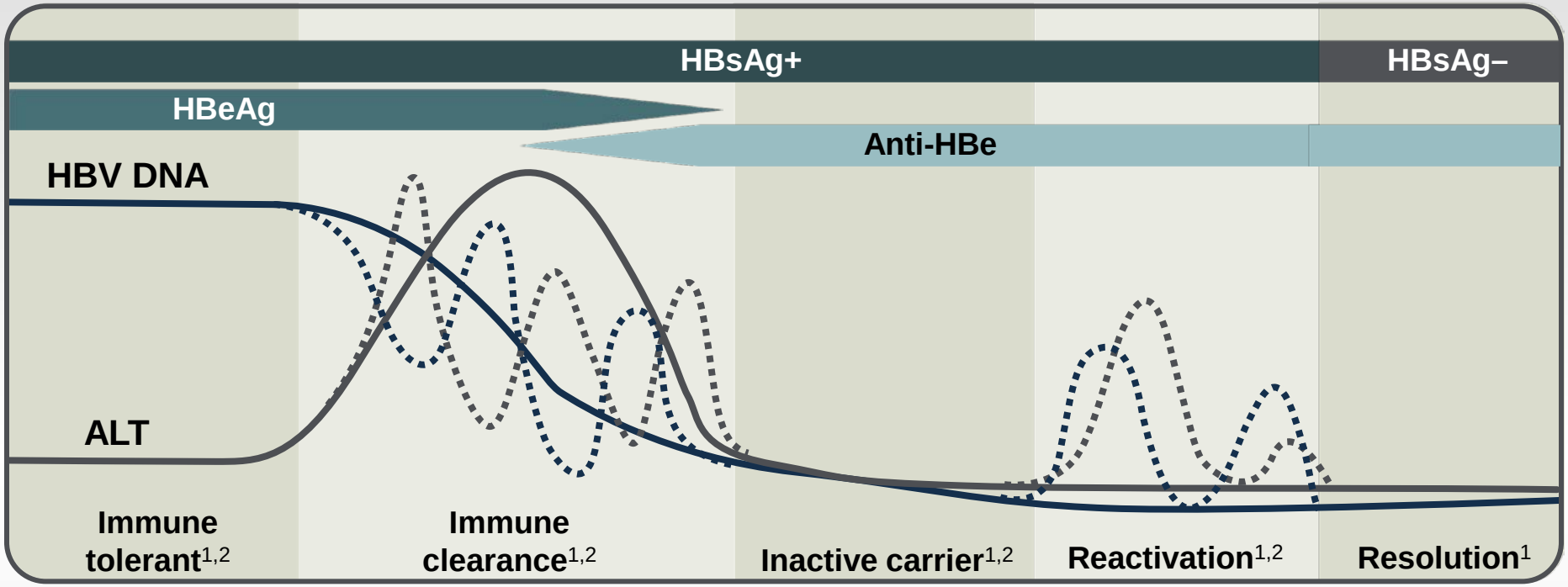
1. CDC. *Morb Mortal Wkly Rep*. 2008;57:1-20.
2. CDC. *Morb Mortal Wkly Rep*. 2005;54:1-31.

Rate of Progression to CHB Based Upon Age at Acute Infection



1. CDC. *Morb Mortal Wkly Rep*. 2008;57:1-20.
2. WHO. Hepatitis B Fact Sheet. http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed October 25, 2011.

Course of HBV Infection



- This phase occurs in patients with perinatally acquired infection
- Minimal or no inflammation
- May last 1 to 4 decades

- High or fluctuating HBV DNA levels
- Persistent or intermittent fluctuation in ALT levels
- Active inflammation and liver damage

- Low or undetectable HBV DNA levels
- Normal ALT levels
- Mild hepatitis, minimal fibrosis, but cirrhosis may be present from previous liver damage

- Some patients may have reactivation of HBV replication
- Usually older patients with more advanced liver disease
- Fluctuating levels of ALT and HBV DNA

- After many years, some patients may enter a resolution phase
- Not considered a "cure" as intra-cellular HBV DNA is still present

Adapted with permission from: Yim HJ, Lok ASF. *Hepatology*. 2006.

CHB follows a nonlinear clinical course; not all patients will go through each phase

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; Anti-HBe, antibody to HBeAg.

1. Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.
2. Yim HJ, Lok ASF. *Hepatology*. 2006;43:S173-S181.

Complications Associated With CHB

Normal	Fibrosis	Cirrhosis	End-stage Liver Disease	HCC
Healthy liver tissue	Consequence of ongoing liver injury and repair[1]	Risk of progression to cirrhosis is 2% to 6% annually[2]	Typically presents 3 to 5 years after a diagnosis of CHB with cirrhosis[2]	Average survival in patients with HCC is ~6 to 12 months, often due to late diagnosis[3]

Up to 40% of patients with CHB will develop cirrhosis, liver failure, or HCC[4]

HCC, hepatocellular carcinoma.

1. Lim YS, Kim WR. *Clin Liver Dis*. 2008;12:733-746.
2. Weisberg IS, et al. *Clin Liver Dis*. 2007;11:893-916.
3. Asian Liver Center. *2007 Physician's Guide to Hepatitis B*. http://liver.stanford.edu/Media/publications/Handbook/2007Handbook.pdf. Accessed October 11, 2011.
4. Lok ASF. *N Engl J Med.* 2002;346:1682-1683.

Host and Viral Risk Factors for HCC

Host Factors

- Male gender[1,2]
- Family history of HCC[1]
- Older age[1,2]
- Coinfection with HCV, HDV, or HIV[1,2]
- Alcohol consumption[2]
- Cigarette smoking[2]

Viral Factors

- HBV DNA levels >2,000 IU/mL (>10,000 copies/mL)[2,3]
- HBV genotype C[2,4,a]
- Basal core promoter mutation[1,2]
- Precore mutation[2,3]
- Presence of HBeAg[2,4]

HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

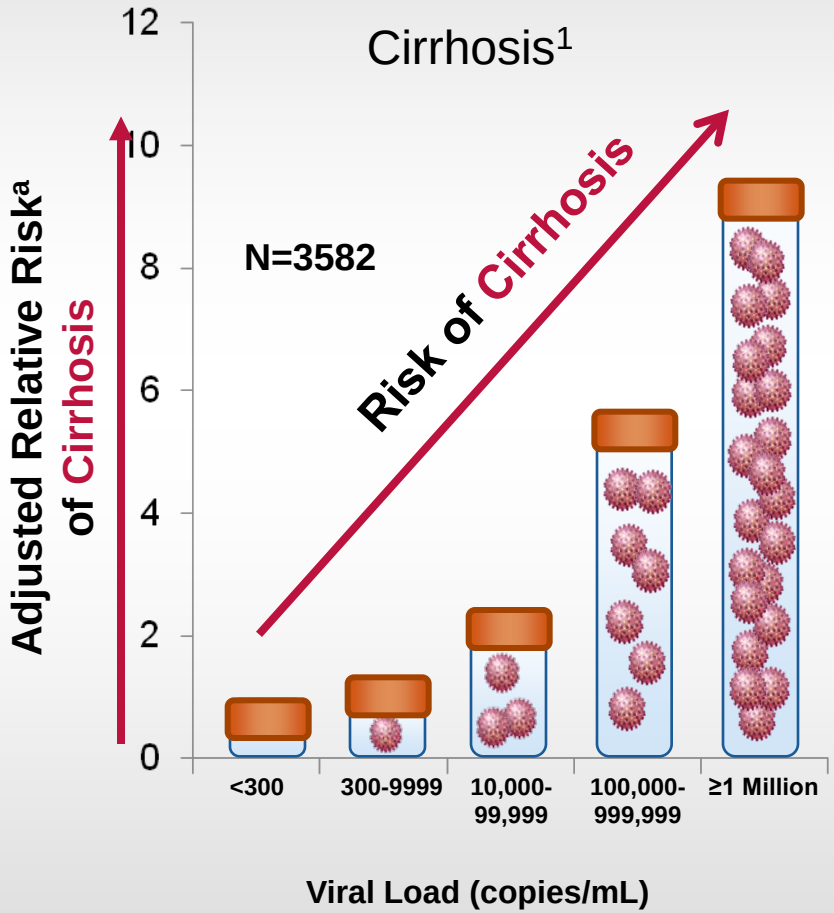
Although cirrhosis is a strong risk factor for HCC, 30% to 50% of HCC associated with HBV occurs in the absence of cirrhosis[1]

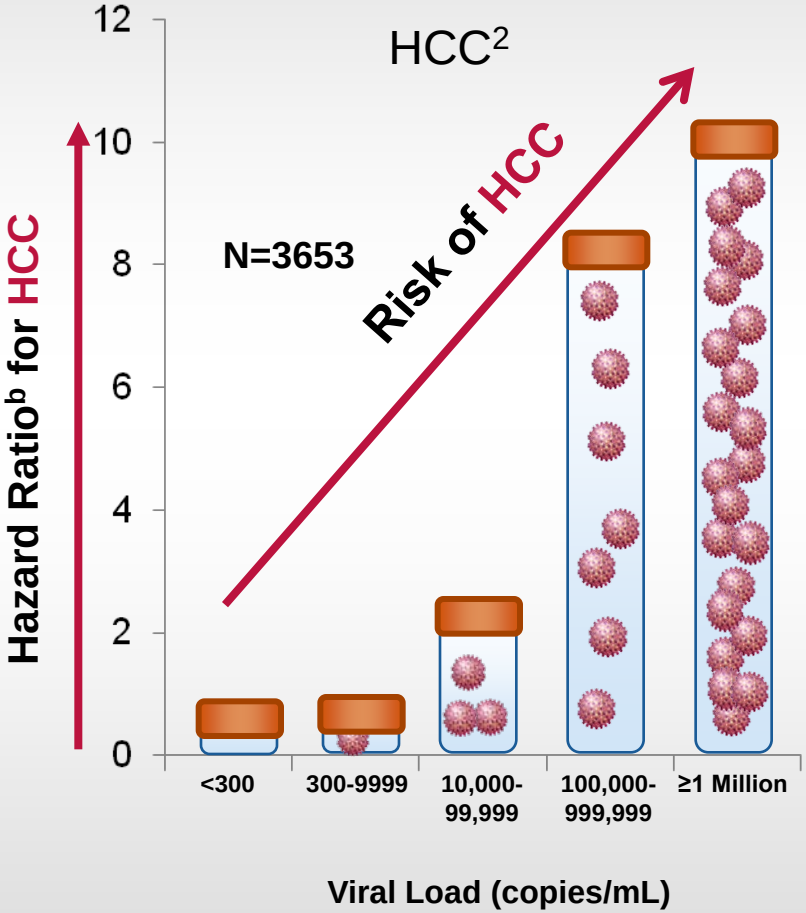
[a]Asian Americans have a higher prevalence of HBV genotype C and a higher risk of HCC than Caucasian Americans.[4,5]

1. Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.
2. Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.
3. Tong MJ, et al. *Liver Int.* 2007; 27:1356-1363.
4. Mahtab MA, et al. *Hepatobiliary Pancreat Dis Int.* 2008;7:457-464.
5. Lin SY, et al. *Hepatology*. 2007;46:1034-1040.

Higher HBV DNA Levels Are Associated With Increased Risk of Cirrhosis and HCC Over Time (REVEAL Study)

Previously untreated patients with CHB





[a]Adjusted for age, sex, cigarette smoking, and alcohol consumption; risk of cirrhosis is independent of HBeAg status and ALT levels.
[b]Relative risk of an endpoint at any given time.

1. Iloeje UH et al. *Gastroenterology*. 2006;130:678-686.
2. Chen CJ et al. *JAMA*. 2006;295:65-73.

Management of CHB

Early Intervention in CHB Can Help Save Lives

SCREEN	Screen and vaccinate all at-risk patients[1,2]
EVALUATE	Evaluate patients who are positive for CHB[1,2]
COUNSEL	Counsel patients at all stages of management[2]
TREAT	Treat with goals in mind[1,2]

Appropriate management is crucial to improve patient outcomes

1. Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.
2. Asian Liver Center. *2007 Physician's Guide to Hepatitis B*. http://liver.stanford.edu/Media/publications/Handbook/2007Handbook.pdf. Accessed October 11, 2011.

Screen

Screen and vaccinate all at-risk patients

Clinical Quiz

Q: Three patients present to a primary care clinic with concerns unrelated to liver disease, whom should you recommend for CHB screening?

	Screen for CHB?	
A 46-year-old woman who immigrated to the US from Nigeria in her early 20s	☑ Yes	☐ No
A 20-year-old man who immigrated to the US from Brazil as a 2-year-old child	☑ Yes	☐ No
A 65-year-old man who has been scheduled to receive chemotherapy for lymphoma	☑ Yes	☐ No

CDC. *Morb Mortal Wkly Rep.* 2008;57:1-20.

CDC Recommendations for Routine CHB Testing

Populations at high risk of CHB include:

- **Foreign-born:** People born in regions of high or intermediate prevalence of HBV infection
- **Children of foreign-born parents:** US-born people not vaccinated as infants, whose parents were born in regions of high prevalence of HBV infection
- **Family and household members:** People whose family or household members have HBV infection
- **Infants born to mothers who have HBV infection**
- **Hemodialysis patients**
- **People with certain medical conditions:** People who need cytotoxic or immunosuppression therapy for a medical condition such as:
  - Cancer that requires chemotherapy
  - Immunosuppression related to organ transplantation
  - Immunosuppression related to rheumatologic and gastrointestinal disorders
- **People with elevated ALT/AST of unknown causes**
- **All pregnant women**

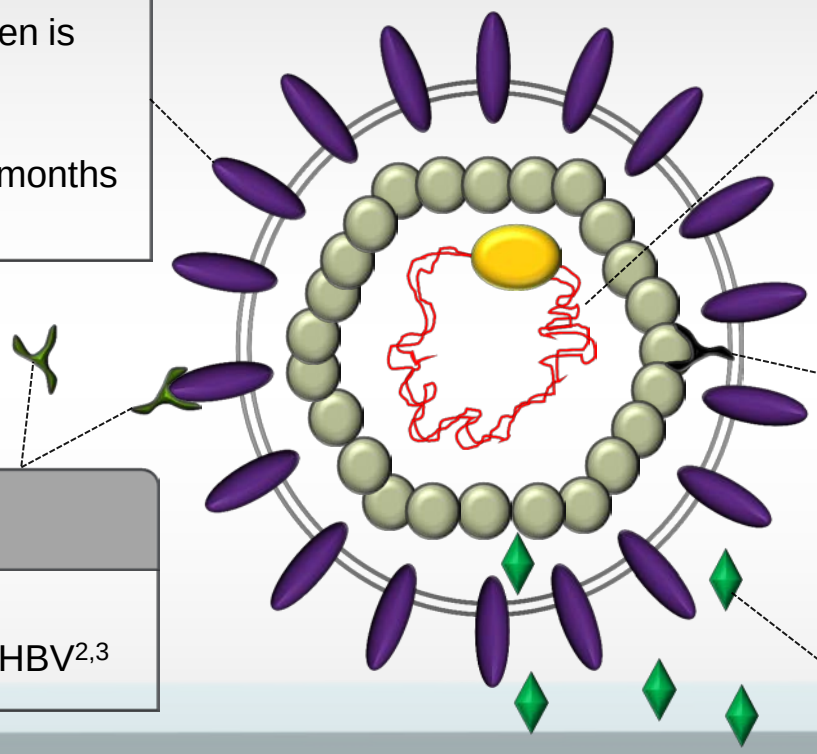
For a complete list of screening recommendations from the Centers for Disease Control and Prevention, please see: CDC. *Morb Mortal Wkly Rep.* 2008;57:1-20.

Serologic Markers in HBV Infection

HBsAg

- The HBV surface antigen is the standard marker of infection[1,2]
- Presence in serum >6 months defines CHB[2]

Hepatitis B Virus



HBV DNA

- Indicates ongoing viral replication[1,2]
- Levels correlate with replication and infectivity[1,2]

Anti-HBc

- Antibody to the HBV core antigen can be used as a marker of infection[2]

Anti-HBs

- Antibody to HBsAg[3]
- Marker of immunity to HBV[2,3]

HBeAg

- Hepatitis B e antigen is used clinically as index of viral replication and infectivity[2,3]

1. Dienstag JL. *N Engl J Med*. 2008;359:1486-1500.
2. Servoss JC, Friedman LS. *Clin Liver Dis.* 2004;8:267-281.
3. Hollinger FB, Lau DTY. *Gastroenterol Clin North Am.* 2006;35:425-461.

Screening for CHB in At-risk Populations

STEP 1 — Screen[1,2]
Order HBsAg and Anti-HBs for ALL patients at risk for CHB

HBsAg	Anti-HBs	Recommended Follow-Up
+	+	CHB present[a]; contact patient for evaluation and further testing; **GO TO STEP 2**
	−	
−	+	Patient has immunity: **No further action required**[b]
	−	Patient at risk for hepatitis B infection; **Vaccinate**[b]

Family and close contacts of people with CHB need screening even if they feel healthy

[a]If patients remain HBsAg-positive for ≥6 months.
[b]Additional testing for anti-HBc is recommended for patients undergoing immunosuppressive therapy or chemotherapy to determine potential risk for reactivation of latent virus.[2]

1. Asian Liver Center. *2007 Physician's Guide to Hepatitis B.* http://liver.stanford.edu/Media/publications/Handbook/2007Handbook.pdf. Accessed October 11, 2011.
2. Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.

Clinical Quiz

Q: What are the next steps in a patient screened for CHB with the following test results?

	Next Steps
HBsAg+ Anti-HBs–	CHB present[a]; further evaluation recommended
HBsAg+ Anti-HBs+	CHB present[a]; further evaluation recommended
HBsAg– Anti-HBs–	Patient potentially at risk for HBV; vaccinate[b]

[a]If patient remains HBsAg-positive for ≥6 months.
[b]Additional testing for anti-HBc is recommended for patients undergoing immunosuppressive therapy or chemotherapy to determine potential risk for reactivation of latent virus.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Vaccination Can Prevent HBV Infection

- The hepatitis B vaccine provides long-term protection for people who have not been infected with the virus
- The hepatitis B vaccine is a series of 3 shots given over 6 months
  - Alternative vaccination schedules given over 4 months demonstrate similar rates of seroprotection

CDC. *Morb Mortal Wkly Rep.* 2006;55:1-40.

Additional Recommended Screening in CHB Patients

Recommended Screening[1]

Hepatitis C Virus (HCV)

- 10% to 15% of patients with CHB are coinfected with HCV[2]

Hepatitis D Virus (HDV)

- A higher proportion of persons with chronic HBV/HDV coinfection develop cirrhosis, hepatic decomposition, and HCC[2]

Human Immunodeficiency Virus (HIV)

- Individuals with HBV and HIV coinfection tend to have more severe liver disease and increased rates of liver-related mortality[2]

Immunity to Hepatitis A Virus (HAV)

- Persons with CHB who are not known to be immune to HAV should be vaccinated[1]

1. CDC. *Morb Mortal Wkly Rep.* 2008;57(RR08):1-20. Accessed September 19, 2011.
2. Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.

Evaluate

Evaluate patients who are positive for CHB

Evaluation of CHB

STEP 2 — EVALUATE
Order HBeAg, HBV DNA, and ALT for ALL patients with CHB

HBeAg	HBV DNA	ALT[a]	Recommended Follow-Up
+	≥20,000 IU/mL	Elevated	**Treat Patient**
		Normal	**Monitor Patient**[b,c]
	<20,000 IU/mL	Elevated	**Monitor Patient**[b]
		Normal	**Monitor Patient**[b,d]
−	≥2000 IU/mL	Elevated	**Treat Patient**
		Normal	**Monitor Patient**[b,c]
	<2000 IU/mL	Elevated	**Monitor Patient**[b]
		Normal	**Monitor Patient**[b,d]

Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

[a]Normal serum ALT values are defined as ≤30 IU/L for men and ≤19 IU/L for women.
[b]Patients with cirrhosis should be considered for treatment regardless of HBV DNA level.
[c]Consider liver biopsy examination, particularly if patient is >35 to 40 years; treat if disease; in the absence of biopsy examination, observe for increase in ALT levels.
[d]Consider therapy in patients with known significant histologic disease, even if low-level replication.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Monitoring CHB in Patients not Recommended for Treatment

HBeAg	HBV DNA	ALT[a]	Recommended Monitoring
+	≥20,000 IU/mL	Normal	• ALT every 3 to 6 months • Consider liver biopsy or treatment if ALT becomes elevated
−	≥2000 IU/mL	Normal	
Other Monitored Patients			
• ALT every 6 to 12 months for inactive carriers • If ALT levels increase, check HBV DNA levels and rule out other causes of disease			

- Significant fibrosis and damage can occur in patients with CHB despite normal ALT levels

Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

[a]Normal serum ALT values are defined as ≤30 IU/L for men and ≤19 IU/L for women.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Recommendations for HCC Surveillance in Patients With CHB

Alpha-fetoprotein and abdominal ultrasound every 6 months

Recommended candidates for surveillance

- Asian men >40 years of age
- Asian woman >50 years of age
- Africans >20 years of age
- Patients with cirrhosis
- Patients with a family history of HCC
- Patients >40 years of age with ALT elevations and/or high HBV DNA levels (>2000 IU/mL)
- Patients 30 to 35 years of age who were infected at birth or in early childhood

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Clinical Quiz

Q: The following test results were obtained when evaluating a 54-year-old Asian woman with CHB. According to the US Treatment Algorithm, what are the next steps?

HBeAg+

HBV DNA = 24,000 IU/mL

ALT >ULN[a]

→

Next Steps

Patient should be considered for antiviral therapy; surveillance for HCC and patient counseling are recommended

ULN, upper limit of normal.

[a]Normal serum ALT values are defined as ≤30 IU/L for men and ≤19 IU/L for women.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Counsel

Counsel patients at all stages of management

Patient Counseling Can Address Barriers to Care

Barriers to screening and treatment for CHB[1,2]

- Limited proficiency in English
- Lack of knowledge about HBV transmission and its consequences
- Lack of health insurance
- Stigma associated with CHB
- Cultural attitudes regarding Western medicine

1. Tran TT. *Cleve Clin J of Med.* 2009;76(suppl 3):S10-S13.
2. Hu K et al. *Dig Dis Sci.* 2011;56:3163-3171.

Patient Counseling Can Address Barriers to Care

Key components of effective CHB counseling[1,2]

- Offer support in patient's own language[1]
- Educate patient that CHB is treatable[2]
- Direct patient to specialists, if necessary[2]
- Consider patient's household and sexual contacts who may be at risk[2]
- Assistance with cost of treatment, if available[2]

1. Tran TT. *Cleve Clin J of Med.* 2009;76(suppl 3):S10-S13.
2. Hu K et al. *Dig Dis Sci.* 2011;56:3163-3171.

Counsel Patients to Prevent Transmission

Persons with CHB should

- Have sexual contacts vaccinated
- Use barrier protection during sexual intercourse if partner not immune naturally or through vaccination
- Not share toothbrushes or razors
- Cover open cuts and scratches
- Clean blood spills with detergent or bleach
- Not donate blood, organs, or sperm

Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.

Reassure Patients

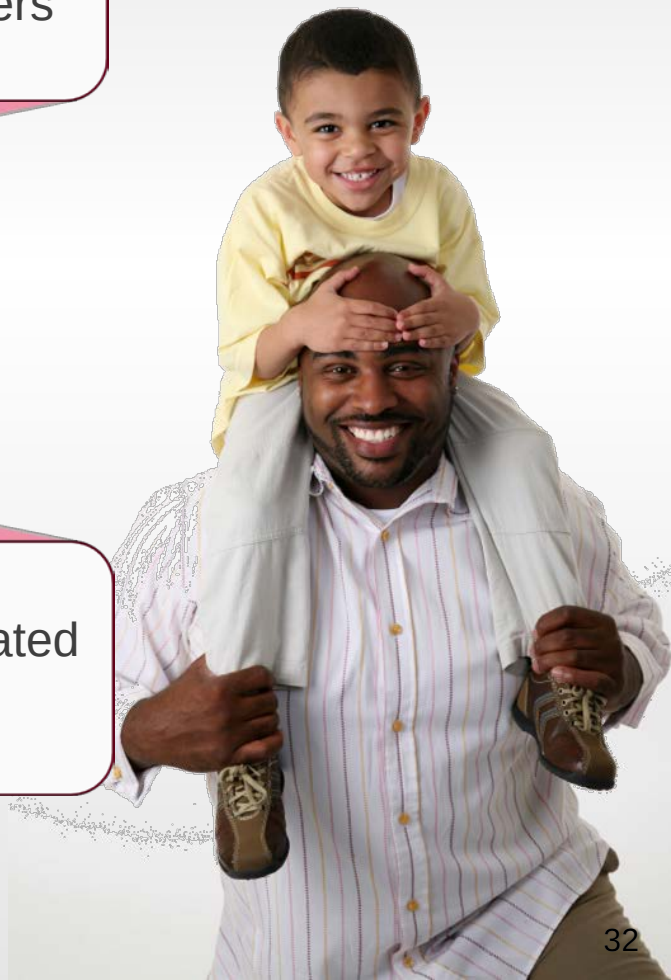
Can participate in all activities including contact sports

Can share food and utensils or kiss others

Children and adults with CHB

Should not be excluded from daycare or school participation

Should not be isolated from others



Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.

Treat

Treat with goals in mind

Treatment Goals

Primary Goal

- Durable suppression of HBV DNA

Other Goals

- Histologic improvement
- ALT normalization
- In patients who are HBeAg+:
  - Loss of HBeAg with seroconversion to anti-HBe

The ultimate aim of treatment is to prevent progression of liver disease to liver failure or HCC and prevent premature death or need for transplantation

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Monitoring Treated Patients

Recommended Monitoring for Treated Patients
• Assess HBV DNA and ALT levels every 3 months until complete virologic response is confirmed • Monitor HBV DNA and ALT every 6 months thereafter

Assessing Treatment Failure/Resistance	
Assess at 3 months:	
Primary treatment failure (HBV DNA decline from baseline <1 $\log_{10}$ IU/mL)	• If patient is compliant, add more potent drug • If noncompliant, counsel
Reassess at 24 weeks:	
Complete response (HBV DNA <60 IU/mL)	• Continue therapy • Monitor every 6 months
Partial response (HBV DNA 60 to <2000 IU/mL)	• Depending on drug profile, monitor every 3 months or add 2nd agent
Inadequate response (HBV DNA ≥2000 IU/mL)	• Add more potent drug; monitor every 3 months
When possible, use agents with low risk for resistance as initial therapy	

Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Stopping Treatment

	When to Consider Stopping Treatment
HBeAg+ (without cirrhosis)	• Continue to treat after HBeAg seroconversion, until HBV DNA levels are undetectable by PCR; treatment then should be continued for an additional 12 months before considering stopping – If HBV DNA levels are still detectable but stable, continue treatment for 6 months; if then HBV DNA levels are undetectable by PCR and HBeAg seroconversion is confirmed, treatment should be continued for an additional 12 months before considering stopping
	• If no HBeAg seroconversion, treat indefinitely
HBeAg– (without cirrhosis)	• Definitive guidelines have not been established; however, long-term therapy is associated with lower rates of relapse
Cirrhosis	• Treatment should be long term • Continue until patient becomes HBV DNA–negative and has lost HBsAg

PCR, polymerase chain reaction.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Conclusions

Conclusions

CHB

- CHB is prevalent in at-risk populations and has serious health consequences[1]
- The majority of those with CHB are undiagnosed and untreated[2,3]

Action

- **Screen** and vaccinate all at-risk patients[4,5]
- **Evaluate** patients who are positive for CHB[4,5]
- **Counsel** patients at all stages of management[5]
- **Treat** with goals in mind[4,5]

Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

1. CDC. *Morb Mortal Wkly Rep*. 2008;57:1-20.
2. Cohen C et al. *J Viral Hepat.* 2008;15:12-13.
3. Cohen C et al. *J Viral Hepat*. 2011;18:377-383
4. Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.
5. Asian Liver Center. *2007 Physician's Guide to Hepatitis B.* http://liver.stanford.edu/Media/publications/Handbook/2007Handbook.pdf. Accessed October 11, 2011